

Investigations into the selective oxidation of vicinal diols to α -hydroxy ketones with the $\text{NaBrO}_3/\text{NaHSO}_3$ reagent: pH dependence, stoichiometry, substrates and origin of selectivity

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Abstract—The $\text{NaBrO}_3/\text{NaHSO}_3$ reagent is one of the few oxidizing agents that chemoselectively oxidizes vicinal diols to α -hydroxy ketones with little overoxidation to the corresponding vicinal-dione or dicarboxylic acid. Oxidation reactions performed with this reagent showed strong pH dependence. *cis*-Vicinal diols reacted faster than *trans*-vicinal diols to the α -hydroxy ketone product. Hydroxy functional groups at axial ring positions were more readily oxidized than equatorial hydroxy groups. The application of the $\text{NaBrO}_3/\text{NaHSO}_3$ reagent for the chemoselective oxidation of vicinal diols was limited to simple systems and failed with more complex monosaccharide compounds probably due to acid catalyzed dehydrogenation reactions. Despite the simple reaction set-up and good selectivity towards the α -hydroxy ketone product, the actual oxidation reaction mechanism is highly complex and postulated to involve at least six different equilibria with a plethora of bromine containing species. A possible oxidation reaction mechanism is discussed.
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1. Introduction

α -Hydroxy ketone (α -ketol) is a functional group entity of natural products with widely studied chemistry.^{1–3} The syntheses of α -hydroxy ketones have been achieved by oxidation of alkenes,^{4,5} by acyloin condensation of diesters,⁶ from enol ethers,⁷ silylenol ethers^{8,9} and epox-

ides¹⁰ or by α -oxidation of ketones^{11,12} and reduction of α -diketones¹³ (Fig. 1). However, the synthetic route through selective oxidation of *sec.-sec.*-vicinal diols has only marginally been covered in the literature.^{14–17} The secondary vicinal diol functionality is a key structural feature in sugars. Selective oxidation of one secondary hydroxyl to a carbonyl function opens the synthetic pathway to pyranose or furanosiduloses also known as ‘oxo’-sugars. To our knowledge, only two methods for this oxidation have been reported in the literature: an enzymatic process involving a rare fungal enzyme^{18,19} and brominolysis of tin-alkyl sugar derivatives.^{20,21} The difficulty in the selective oxidation of a vicinal diol to the corresponding α -hydroxy ketone is the prevention of overoxidation to a vicinal dione or—after C–C bond cleavage—dicarboxylic acid (Scheme 1). Assuming a first order reaction rate of the bimolecular reaction between the OH-compound, i.e. vicinal-diol or α -hydroxy ketone, and oxidizing species the relative ratio of the reaction rate constants k_1 (diol \rightarrow α -OH-ketone)/ k_2 (α -OH-ketone \rightarrow dione) has to be ≥ 10 to support a synthetically useful selectivity discrimination between the

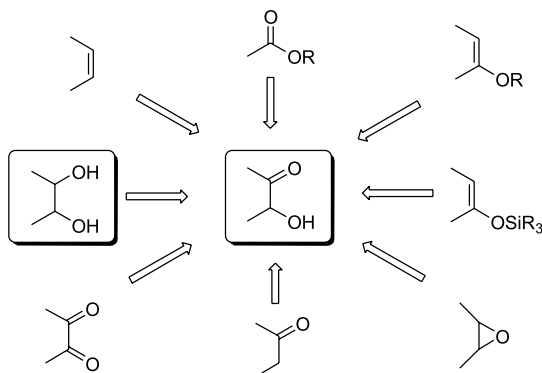
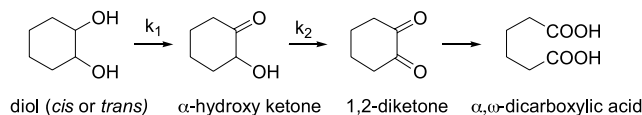


Figure 1. Synthetic routes to α -hydroxy ketones.

Keywords: Chemoselective oxidation; Vicinal diols; α -Hydroxy ketone; Hypobromous acid.

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Scheme 1. Oxidation of vicinal diols.

α -hydroxy ketone and the vicinal-dione compound.^{22,23} This requirement is probably one of the reasons why the chemoselective oxidation of *sec.-sec.-vicinal* diols is limited to only few methods with Ishii's NaBrO₃/NaHSO₃ reagent being one of them.²⁴

The simple oxidation reaction conditions for the NaBrO₃/NaHSO₃ reagent are particularly useful for organic syntheses as the chemicals are commercially available and inexpensive off-the-shelf compounds. Yet, the actual reaction mechanism is very intriguing and displays good chemoselectivity. In a remarkable methodology, a mild oxidizing agent is generated in situ by addition of both, an oxidant, sodium bromate, and a reductant, sodium bisulfite. Ishii et al. postulated that the actual oxidant was hypobromous acid, HOBr, as bromohydrins are formed in reactions involving C=C bonds.^{24,25} The NaBrO₃/NaHSO₃ reagent has also been successfully employed in the γ -lactone formation of *o*-alkyl substituted benzoic acids.²⁶ Other reactions that make use of bromate together with reducing agents are the Belousov–Zhabotinskii class of oscillating reactions.^{27,28} Metsger et al. reported that the oxidation of alkyl ethers occurred in α -position by Br₂, which is generated through the comproportionation reaction of bromate and bromide to provide a low but steady concentration of bromine.²⁹

Here we report additional insights into the selective oxidation of vicinal diols to the corresponding α -hydroxy ketones using the NaBrO₃/NaHSO₃ reagent, specifically its scope and limitations with respect to pH, diol substrates, its reaction mechanism and the origin of the chemoselectivity.

2. Results

Oxidation reaction experiments were conducted on a small scale (4.2 mL, 0.24 M diol substrate) and monitored by quantitative gas chromatography calibrated against dimethyl sulfone as the internal standard. Oxidation products were identified by GC-MS and by comparison with authentic commercial samples when available. The oxidation experiments of the monosaccharide substrates were conducted on an NMR scale in D₂O (0.7 mL, 0.24 M substrate) and directly monitored by ¹H and ¹³C NMR spectroscopy.

2.1. pH dependence

The oxidation reaction of *trans*-1,2-cyclohexanediol exhibited a strong pH dependence (Table 1), an important observation that has previously not been reported. The reaction stoichiometry of diol substrate, sodium bromate and sodium bisulfite was adopted from the established oxidation procedure published by Ishii et al.²⁴ Entry 2 corresponds to the reaction condition reported by Ishii et al., resulting in an initial pH of 1.7.²⁴ Changes of the pH of the reaction solution were effected by addition of sulfuric acid or Na₂HPO₄. The desired α -hydroxy cyclohexanone product was generated almost quantitatively within 1 h to 24 h while the overoxidation product, 1,2-cyclohexanedione, was only present in 0–5%. It was found that the oxidation reaction proceeded only in acidic solution at pH

Table 1. pH dependence of the effectiveness of the NaBrO₃/NaHSO₃ reagent in the oxidation of *trans*-1,2-cyclohexanediol^a

Entry	pH _{initial}	pH _{final}	α -Hydroxy cyclohexanone % (t) ^b
1	0 ^c	0.5	95% (1 h)
2	1.7	2.3	74% (4 h) 97% (24 h)
3	2.3 ^d	2.8	25% (4 h) 70% (24 h)
4	4.0 ^d	4.4	No reaction (48 h)
5 ^e	5	5	No reaction (48 h)
	1.7 ^f	2.3	74% (4 h) 97% (24 h)

^a Reaction conditions: 1.0 mmol diol, 1.2 mmol NaBrO₃, 1.2 mmol NaHSO₃ in 2.2 mL H₂O and 2.0 mL CH₃CN at 21 °C ± 1 °C.

^b Determined by GC. Content of 1,2-cyclohexanedione was <5%.

^c H₂SO₄ added until desired pH_{initial} value reached.

^d Na₂HPO₄ added until desired pH_{initial} value reached.

^e 1.2 mmol Na₂SO₃.

^f Addition of 0.6 mmol H₂SO₄.

values <4 and that the oxidation reactions were faster at lower pH. When the oxidation was completed the final pH values of the reaction solutions were higher than the initial pH values by approximately 0.5 units. In a control experiment, Na₂SO₃—instead of NaHSO₃—was reacted with sodium bromate and no reaction occurred within 48 h (Entry 5). With *trans*-1,2-cyclohexanediol as the substrate, a reaction solution containing Na₂SO₃ and NaBrO₃ had an only slightly acidic pH of 5. When this reaction solution was subsequently acidified with 0.5 equiv of conc. sulfuric acid (0.6 mmol, 1.2 equiv of H⁺) resulting in pH of 1.7, the oxidation reaction immediately proceeded as with the original NaHSO₃/NaBrO₃ reaction condition (Entry 2).

2.2. NaBrO₃/NaHSO₃ reagent stoichiometry

Various bromate and bisulfite amounts were added to *trans*-1,2-cyclohexanediol substrate in order to investigate the optimum oxidation reaction condition for the NaBrO₃/NaHSO₃ reagent (Table 2). Ishii et al. reportedly applied equal molar sodium bromate and sodium bisulfite quantities in slight excess with respect to the diol substrate (Entry 2).²⁴ Throughout all reactions (Entries 1–12), the initial concentration of *trans*-1,2-cyclohexanediol (0.24 M, 1.0 mmol) was held constant and yields of α -hydroxy cyclohexanone were determined by quantitative GC analysis. Generally, it was found that even with more equivalents of oxidant, the 1,2-cyclohexanedione yield was not significantly increased always remaining in the range of 0–5%. Addition of an equimolar ratio of NaBrO₃ and NaHSO₃ in half to three equivalents with respect to the diol substrate generated the α -hydroxy ketone quantitatively within 2–120 h (Entries 2–4). The 1,2-cyclohexanedione content was 15% at the extended reaction time of 120 h (Entry 1). No reaction—neither oxidation nor reduction—of *trans*-1,2-cyclohexanediol occurred when sodium bromate and sodium bisulfite were added individually (Entries 5 and 6). The oxidation reaction leveled off at 51% conversion after 48 h when the relative ratio of bromate and bisulfite was 0.6–1.2 mmol (Entry 7). However, addition of 1.2 mmol bromate and 2.4 mmol bisulfite to the diol substrate completed the oxidation reaction within 24 h (Entry 9). An oxidation reaction was not observed when the NaBrO₃:NaHSO₃ ratio was less than 1:3 (Entries 10–12). Quantitative oxidation

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